Protocol for a Radiological Study of Silicosis in Industrial Sand Workers

I. Background and Purpose of the Study

The primary goal of the proposed exposure-response study is to assess the relationships between individual estimates of quartz exposures in workers at two industrial sand companies and changes on chest X-rays characteristic of silicosis. It will employ a nested case-control design, which has the advantage of providing estimates that are comparable to a prospective analyses based on the entire cohort without a substantial reduction of statistical power. The study will also include an examination of exposure in relation to radiologic changes indicative of progression in those workers identified as having radiologic silicosis. The goal will be achieved by accomplishing the following specific aims.

1. Conduct radiological film reading studies to (a) verify the presence of radiologic silicosis in cases and its absence in controls at the time the case was found to have changes and (b) determine radiologic changes occurring in cases after first detection of radiologic silicosis.
2. Estimate yearly exposures to respirable quartz (RQ) experienced by cases and controls.
3. Determine the relationships in these workers between radiographic changes consistent with silicosis and cumulative exposure, average exposure and duration of exposure to RQ, both with and without the use of a lag to account for the time between exposure and development of radiographically detectable silicosis.
4. Examine exposure-response relationships using other metrics to model the effects of the timing of exposure, changes in intensity over time, and potential thresholds for quartz exposure and radiologic silicosis.
5. Use the exposure-response relationships from this study to estimate the absolute risks of developing radiologic silicosis at occupational exposure limits of 0.05, 0.1 and 0.2 mg/m^3 quartz over a working lifetime.
6. Determine the relationship between exposure, level of opacity at first detection and progression in workers with workers with radiologic silicosis.
7. Compare exposure- response estimates for risk of disease and probability of progression derived from this study to those of other published studies.

The primary hypotheses to be tested by the study are as follows:

1. The relative risk of radiologic silicosis increases with increasing average exposure, cumulative exposure and duration of exposure.

2. Exposure response-relationships that include a threshold fit the data better than those that do not.

3. Estimates of the absolute risk of radiologic silicosis at lifetime occupational exposure limits of 0.5 and 0.1 mg/m^3 do not differ significantly from zero.

4. Progression of radiologic silicosis depends on exposures occurring both before and after the date it is first detected.

5. The level of radiographic opacity at first detection is predictive of silicosis progression.

Despite the many published studies of exposure-response relationships for quartz and radiographic evidence of silicosis, there is considerable disagreement in the risk estimates for what could be considered equal exposures to quartz. These uncertainties may be due at least in part to weaknesses in previous studies. Some limitations that can be improved upon in this proposed study of industrial sand workers include:

- Lack of reliable information about the risk of radiologic silicosis at low levels of exposure.
- Estimates from some studies were based on exposures to extremely high levels of quartz, such as those observed in the Scottish coal study.
- Limited quality of exposure data for early exposure years, such as those in the Colorado hardrock miners study.
- Exposure estimates in some studies were based on only one early study and exposures were not expressed in quartz concentrations.

The weaknesses of these earlier studies can be improved upon with the proposed study because of better exposure data and radiographic film surveillance.

- Both of the participating companies have thousands of exposure measurements for quartz that date back to the 1970s.
- Measurements are in mass concentration units (milligrams per cubic meter) of respirable quartz.
- Exposure samples encompass a large number of job codes with low to high quartz concentrations, which should ensure a wide range of exposures for analyses of exposure-response.
- Data were collected in a systematic manner over a long period with personal identifiers that will facilitate construction of a job-time-exposure matrix.
- The quartz concentrations in the exposure databases for this study were all conducted using X-ray powder diffraction analytical methods which are superior to earlier methods used to quantify quartz concentrations.
- The companies have all conducted periodic medical surveillance (every two years) since the late 1970's and most of the study subjects have more than 10 serial films in their surveillance files.

The study population are production workers from two industrial sand companies who have worked for $\geq$ 10 years and have a posterior-anterior (PA) chest X-ray taken as part of their company surveillance program $\geq$ 10 years after hire date. The ten year criterion was chosen because it is the latency period often used by the National Institute for Occupational Safety and Health (NIOSH) and others as the period required for the development of silicosis. The dust data from these companies have been previously analyzed for epidemiological studies and we are

confident exposures are not of the magnitude to result in accelerated or acute cases of silicosis. The cases and their matched controls will come from 14 different plants in 10 states.

II. Proposed Methodology

A. Data Collection, Handling and Worker Notification.

In 1977, the National Industrial Sand Association (NISA) adopted a silicosis prevention program which prescribes guidelines for its member companies to use in conducting dust exposure surveillance and medical surveillance for their workers. In 1997, NISA revised and published its guidance in Occupational *Program for Exposure to Crystalline Silica in the Industrial Sand Industry*, which was revised again in 2009.[1] The guidance included in the program reflects the recommendations of health research organizations such as the American Thoracic Society (ATS) and the NIOSH, and regulatory agencies, such as the Mine Safety and Health Administration (MSHA) and the Occupational Safety and Health Administration (OSHA). NISA member companies use the program to engage in monitoring of quartz exposures and medical surveillance of their employees both to control exposure to quartz and to provide a data base for future epidemiological studies. There have been four epidemiological studies sponsored by NISA that have made use of these databases.[2, 3, 4, 5] The two companies participating in this study have implemented the elements of the program beginning in 1977 and have maintained systematic databases of the information gathered under this program since its inception.

The dust monitoring program contains detailed information on collecting respirable dust samples for quartz analyses using personal and area sampling procedures. The manual covers topics such as sampling procedures, sampling equipment and calibration, analytical procedures and laboratory selection, data sheets and sampling records, sampling frequency, interpretation of results, statistical management of data, and worker notification. Using these guidelines the two

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[1] Reference National Industrial Sand Association (2010). The *Occupational Health Program for Exposure to Crystalline Silica in the Industrial Sand Industry.* Washington, DC.

[2] McDonald, AD, McDonald, JC, Rando, RJ, Hughes, JM and Well, H (2001). Cohort mortality study of North American industrial sand workers. I. Mortality from lung cancer, silicosis and other causes. *Annals of Occupational Hygiene,* 45, 193-9.

[3] Hughes, JM, Weill, H, Rando, RJ, Shi, R, McDonald, AD and McDonald, JC (2001). Cohort mortality study of North American industrial sand workers. II. Case-referent analysis of lung cancer and silicosis deaths. *Annals of Occupational Hygiene,* 45**,** 201-7.

[4] Rando, RJ, Shi, R, Hughes, JM, Weill, H, McDonald, AD and McDonald, JC (2001). Cohort mortality study of North American industrial sand workers. III. Estimation of past and present exposures to respirable crystalline silica. *Annals of Occupational Hygiene,* 45, 209-16.

[5] McDonald JC, McDonald AD, Hughes JM, Rando RJ, Weill H. Mortality from lung and kidney disease in a cohort of North American industrial sand workers: an update. Ann Occup Hyg. 2005 Jul;49(5):367-73.

companies have collected over 49,000 personal samples. Exposure reconstruction for the cases and controls will be made from this extensive dust monitoring database.

Production employees of the participating companies are required to take part in the periodic health surveillance offered by the companies. The initial chest radiograph is taken at a local radiology facility and periodic chest X-rays are taken in a mobile medical coach. A radiologist certified by NIOSH as a B Reader interprets the radiograph for clinical changes and provides an International Labor Organization (ILO) Classification of his findings. Positive films and a percentage of negative films are classified by a second B Reader, and a third B Reader if necessary to resolve disagreements. Workers are notified of the results of the radiographic interpretations. The companies are notified of the results of the radiographic interpretations, own the X-ray films, and store them for future medical consults and studies, such as the one proposed. This repository of chest X-rays will be used for the radiographic studies.

The cases for the study will be identified from approximately 1,670 eligible production workers at the two participating companies, working at 14 different plants in 10 states. They will have worked for $\geq$ 10 years and have a posterior-anterior (PA) chest X-ray taken as part of the company surveillance program $\geq$ 10 years after hire date. The cases will be identified from a radiological review and re-classification of the last film in the series of surveillance films for each eligible worker. For each case identified from re-reading the last film in the series, all films will be reviewed to determine the date of the X-ray with the earliest changes consistent with radiologic silicosis (see section II.B.a.). Three workers controls will be randomly selected from all workers at the same plant who were born within three years of the case and had an X-ray with no evidence of silicosis on or after the date of diagnosis for the case. If an employee is a possible match for a case but that employee later becomes a case himself (i.e., develops X-ray changes indicative of silicosis), that person will still be eligible to be a match for that case. This sampling strategy is an essential feature of a nested case-control design to eliminate selection bias.

Work histories will be compiled by company human resources, and safety and health professionals. The human resource files are very complete and have been used to develop work histories for a job exposure matrix in previous studies. A study researcher will visit the company offices to verify the adequacy of work history compilation for a percentage of cases and controls.

Each study subject will be assigned a unique study identification number that will be used in all computer files and on labels affixed to the study X-rays. Only study investigators and staff will view any forms containing personal identification of study subjects (e.g., job histories). All such forms will be stored in locked files for the duration of the study and will be shredded upon completion of the study.

Employees will be informed that a study is being conducted to assess whether chest X-ray changes are related to crystalline exposure concentrations. They will be assured that only the

investigators (and their staff) will view individual data and that all reports will only contain statistical summaries, with no possibility of identification of individuals. If the study identifies a chest film abnormality that was not previously detected and reported to the employee by the physician retained by the company, then a report will be sent to the employee, along with a recommendation that he consult with his local physician.

The two companies involved in the study have conducted respiratory medical surveillance for their workers since the late 1970s, have informed the workers of results, and have used the results of the program, especially the radiographic results, to manage the exposures to workers with radiological changes consistent with silicosis. The results from re-classification of the films on these workers will be subjected to multiple ILO classifications by academic radiologists, and they should therefore be more clinically precise than those obtained from the routine medical surveillance classifications. Because the results of the individual classifications could be useful in managing the silicosis risk to workers, the Principal Investigator will provide the results to the respective company's medical coordinator for entry in each individual's medical file.

In addition, employees will be informed upon completion of the study with respect to risks related to quartz exposure. A study investigator(s) will visit one, or more, of the larger plants of each company, present the study's overall findings and answer questions from employees. Results concerning quartz exposure concentrations observed in the plants will be compared with the exposure concentration limits currently in place under the Mine Safety and Health Administration regulations and the NIOSH Recommended Exposure Limit for crystalline silica. A video will be made of one or more of these presentations and the video shown to employees of smaller plants.

B. Radiological Classification Protocol

Chest radiography is the most common method of screening for silicosis in industries where quartz exposures occur. Radiographic changes of silicosis are generally seen before abnormal decline in pulmonary function or symptoms are detected. Chest X-rays for the pneumoconioses (e.g., silicosis, coal workers pneumoconiosis, and asbestosis) are classified by an internationally recognized system developed by the ILO. The ILO system provides a means of systematically classifying a chest X-ray according to parenchymal (i.e., the alveolar tissue of the lung) and pleural (i.e., the membranous lining of the lungs) findings. Parenchymal abnormalities (small and large pneumoconiotic opacities) are commonly caused by crystalline silica exposure. Pleural changes are not considered to be related to crystalline silica exposure but are most commonly regarded as a marker of exposure to asbestos or are caused by other disease processes. Pleural changes reported in this study are a medical finding of interest but will not be included in any analyses.

The characteristic radiological abnormality seen in workers with simple silicosis consists primarily of small rounded well-circumscribed nodules occurring bilaterally in the upper and mid zones of the lungs. [6, 7] Simple silicosis is said to be present when a profusion of small opacities (1/0 to 3/+) exists, and complicated silicosis is said to occur when large opacities are present (A, B or C). Classifications for epidemiological purposes require that all appearances described in the ILO Guidelines and seen on the standard radiographs are to be classified. Symbols and comments will be used to record other appropriate findings. A large opacity is considered to be present when an opacity presents its longest dimension exceeding 1 centimeter and is evident on a chest film in which there is sufficient evidence to suggest the presence of pneumoconiosis. The classification allows the reader to also identify non-pneumoconiotic large opacities due to other causes such as lung cancer. Large opacities are codified in three categories, depending on the size of the lesions.

Because variability in radiographic classifications for pneumoconioses is well documented each film will be independently classified by three "blinded" B Readers board-certified in radiology. The principal investigator and research team will conduct the film classification studies with the radiologists at a central location. The principal investigator and research team will closely hold and retain all study materials and the participating radiologists will be told only what is required to achieve the ILO classification of films. The final profusion classification will be reached by using a median reading of the three independent readings. If any film is classified as unreadable (UR) by two of the three radiologists that film will be removed from the study and not analyzed since a median classification cannot be determined. If any film is classified as unreadable by one of the three radiologists and the other two radiologists agree as to profusion subcategory the agreed to classification will be scored. If any film is classified as unreadable by one of the three radiologists and the other two radiologists are **not** in agreement as to profusion subcategory, that film's profusion will be classified as the midpoint subcategory between the two readings if their profusion classifications are separated by an odd number of subcategories. If separated by an even number of subcategories then the classified profusion will be assigned randomly to the higher or lower ILO subcategory of the two classifications. If two profusion classifications are adjacent subcategories the classified profusion will be randomly assigned to the higher or lower ILO subcategory of the two classifications.

The three radiologists involved in classification of films will be currently certified as a NIOSH B Reader and academic thoracic radiologist. All classifications will be determined in an independent manner; without conferences between the radiologists. Standard 2011 ILO reference radiographs will be used by all expert radiologists. The complete, as opposed to the abbreviated, version of the 2011 ILO classification system is to be used, including specified

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[6] Henry DA, International Labor Office Classification System in the Age of Imaging: Relevant or Redundant. (2002). Journal of Thoracic Imaging; 17:179-188.

[7] Kim KI, Chang WK, Lee MK, et al. (2002). Imaging of Occupational Lung Disease. RadioGraphics; 21:1371-1391.

findings such as film quality, profusion of and categorization of parenchymal abnormalities, any pleural findings, large opacities and incidental findings as obligatory symbols and/or comments. Each blinded radiologist will be given no information whatsoever regarding the provenance of the films, purpose of the survey, background of the cases, potential exposures to pneumoconiotic dusts, names of the subject, dates of the examination, X-ray facilities, and initial readers' results. The radiologists are to use the instructions set forth in the 2011 ILO classification system.

All personal and identifying information on all chest films will be covered over by the research team and replaced by a code number known only to the principal investigator and appropriate researchers. In addition, any film that has been marked on in a previous reading (by grease pencil or other marker) will not be classified unless the markings can be removed to the satisfaction of the principal investigator. Each film and matched classification forms will be assigned a set code number by the principal investigator and will be used for linkage to classification forms. A blank film jacket will be substituted for the jacket in which each film was received. The expert radiologists will not keep copies of their classifications. After the classifications are completed the principal investigator will be responsible for collecting all ILO classification forms, stripping the films of their study identifiers, re-sleeving the films in their original jackets and returning all films to the respective companies

a. Radiological Identification of Cases

Cases with radiologic abnormalities consistent with pneumoconiosis will be identified by classifying the last film in the series of surveillance films for each worker eligible for the study (approximately 1670 workers). For this phase of the study a member of the research team (JEP) who is a NIOSH certified B Reader and has extensive experience in classifying films using the ILO guidelines will provide the initial classification for all films. A second classification of films of eligible workers will be made by a NIOSH certified B Reader who will not participate in further classification phases of the study. If the initial two classifications do not agree on minor category of profusion those films will be sent to a third NIOSH certified B Reader who will not participate in further classification phases of the study. The ILO profusion classification will be considered the median profusion classification. To be more sensitive in identifying cases for the case-control study the criteria for case identification will re-classify the last film for each worker and will accept both rounded and irregular small opacities regardless of whether the predominant shape factor is rounded.

For the cases identified in this phase of the study, all of the surveillance films will be pulled. The series for each worker in chronological order will be reviewed by JEP to identify the first film in the series where changes consistent with pneumoconiosis (small rounded and irregular opacities) occur. The film for each worker where earliest changes occur will determine the date of first detection of radiologic pneumoconiosis for the case-control study. This date will be used for identification of eligible controls for each case in the case-control study. If an

employee is a possible match for a case but that employee later becomes a case himself (i.e., develops X-ray changes indicative of pneumoconioses), then that person will still be eligible to be a match for that case.

The data from this phase will be tabulated but will not undergo further analyses related to exposure-response relationships.

b. ILO Classification of Chest X-ray Films

The films on cases, matched controls, and serial films on cases will be independently classified by three "blinded" B Readers board-certified in radiology. The principal investigator and research team will conduct the film classification studies with the radiologists at a central location. ILO classification according to the 2011 guidelines will be made for each film and the classification forms will be used for analyses of results. The 12-point ILO profusion classification system will be converted to numerical digits for analyses by designating 0/- as number 1 continuing through the system with 3/+ designated as 12. Grouping of films for the ILO classification will be batched to facilitate exchanging films among the readers but will not necessarily be of the same size.

The case film for classification in this phase of the study will be identified as discussed in II. C. above. For matched controls we will select the film with the closest date in the film series of the control on or after the date of the case film considered consistent with pneumoconiosis. All cases will be included in the progression classification. For all cases every film taken as part of the medical surveillance program will be pulled from each company's repository and included in the progression study. However, there are a number of workers that have had films taken annually after identification of a positive film. For these workers, every other film will be classified in the progression study.

The final small opacity profusion determination on a given film will be the median profusion of small opacities so as not to give undue weight to either unusually high or low profusion classification. The classification of radiological silicosis for purposes of data analyses will be small opacities classified with a profusion of $\geq 1/0$ and shape factor of predominantly rounded shape (irregular can be the secondary shape factor, e.g., p/s, q/t, etc.) occurring in any of the six lung zones and/or a large opacity of size A, B or C. All appearances described in the guidelines will be classified. If any of the appearances of the parenchyma or pleura are not consistent with pneumoconiosis and were the result of some other etiology appropriate symbols and comments are to be made on the classification form. Large opacities will be determined if at least 2 out of 3 radiologists are in agreement as to presence of an opacity in which there is sufficient evidence to suggest the presence of pneumoconiosis. Non-pneumoconiotic large opacities of other causes will not be entered for analyses. If there is disagreement as to size of a large opacity the median of the three radiologists will be recorded. If only two radiologists classify a film with large opacities and the third classifies the film as unreadable the large opacity

classification will be assigned randomly to the higher or lower opacity and opacity size will be recorded. All chest X-rays will be classified into the 12-point classification for small opacities.

c. Estimate of Chest X-Rays for Classification Studies

There are ~2,051 chest X-rays on industrial sand workers that meet the inclusion criteria for the study. To identify the cases for the study each eligible worker will have two independent ILO classifications of the last film in their surveillance film series. To resolve disagreements of a subcategory of profusion a third independent classification will be obtained. It is estimated this step will require ~4,175 independent classifications.

Assuming that 75 cases are identified, 225 randomly matched controls are selected and 25 quality assurance films are inserted will result in a total of 325 films. Three independent classifications will be needed for a total of 975 independent classifications. Serial films for cases will be included in the progression films. Assuming 75 cases with 10 serial films each will result in 750 films. Each film will require three classifications for a total of 2,250 independent classifications. Thus, each radiologist will classify 1,075 chest x-rays.

Some of the early films of the surveillance films may have deteriorated in storage to the extent they will not be able to be classified.

C. Exposure Reconstruction

All of the companies involved in the proposed study have been taking routine personal samples of workers for respirable RQ. The data are in electronic format, although there are differences in formatting among the two companies involved in this study. The databases of the industrial sand companies have been used in previous mortality and morbidity studies, some conducted by the current investigators, and this will facilitate their use for exposure reconstruction in the proposed project. In addition to company databases, quantitative and qualitative data will be obtained from other sources such as consultant reports, government reports, and government databases. The researchers will decide on the significance of these data in constructing the job/time/exposure matrix for each plant. Certain plants may have been in operation before being acquired by the companies involved in this project. For such plants, there may be little information about prior exposures in currently existing corporate exposure monitoring databases. In these cases, we will work with our corporate liaisons to identify and acquire any information on dust levels that predates the corporate acquisition of the plant in question, such as the public archives of the federal Mine Safety Health Administration and its predecessor.

For each plant, a separate job/time/concentration matrix will be developed for the time period beginning with earliest date of hire of participating workers, to the study cutoff date. The matrix will be developed using an approach similar to that employed in our previous studies of

RQ levels in the industrial sand industry.[8] The job exposure matrix will then be integrated with the specific job histories of the participating workers to calculate yearly exposures for each individual, which will be used to compute cumulative and average exposures to RQ, as well as other exposure metrics. It is anticipated that for the plants and workers from the industrial sand industry segment, the focus will be primarily on updating exposure information previously gathered and analyzed in prior epidemiologic studies conducted by Tulane researchers. The components of this approach are described below.

Plant information: For each plant, we will request the following information: a process flow schematic, breakdown of jobs and departments/areas, and a history of major process or engineering changes with an emphasis on those that may have altered dust concentrations in the workplace. Questions concerning the received information will be resolved through discussions with corporate or plant personnel. It is not anticipated that any plant visits will be necessary since the exposure reconstruction researcher has visited many of these industrial sand facilities in conducting previous studies and is thoroughly familiar with the processes, operations and jobs in the plants under study.

Job histories: Complete job histories for all participating workers will be developed by the participating companies and will be provided to the Tulane researchers. These job histories shall include date of initial hire with the company along with job title and department or work area. All subsequent changes in job title, with corresponding dates of initiation/termination shall be included. It is expected that the companies will develop the job histories by in-house review of their personnel and employment records and supplement as needed with discussions with the employees and their supervisors. We will provide a job history computer template to the participating plants to ensure uniformity and completeness in developing the information.

Upon receipt, the Tulane researchers will review the job histories with the aim of identifying and correcting any errors, obtaining any missing information, and harmonizing the listings for all participating workers in a plant. We will then code each job listing with unique identifiers for each job title at a facility. The coding system will match that used in the job/time/concentration matrix. Ten percent of the job histories will be verified by the principal investigator by examining company records that served as the basis for development of job histories.

Development and application of the matrix: A dictionary of job codes for each plant will be developed after careful review of the respective job history profiles, and current and historical plant and process information. Job listings will be collapsed into unique groupings as appropriate in order to eliminate duplication and maximize statistical power in estimating average concentrations for all jobs in a given similar exposure group. In particular, we will

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[8] Rando RJ, Shi R, Hughes JM, Weill H, McDonald JC, McDonald AD: Cohort Mortality Study of Silicosis and Lung Cancer in North American Industrial Sand Workers. III. Estimation of Past and Present Exposures to Respirable Crystalline Silica. Ann. Occup. Hyg., 45:209-216, 2001.

carefully investigate the frequency of cross-over among job titles and tasks within plant departments. Previous experience found this to be a common occurrence in some situations. In such scenarios, it is appropriate to assign a department-wide job code and corresponding average concentration, for all workers involved, regardless of job title.

Estimates of average exposure to RQ for each job code will be taken as the arithmetic mean concentration calculated from the monitoring data over an appropriate time segment in which the concentrations are judged to be stable. This will be determined by examination and identification of any temporal trends or changes in the monitoring data using traditional statistical tests (t-test, ANOVA, regression) on the log-transformed concentration data. Identified changes will be correlated with the known timing of changes in process, work practices, and dust controls. In those cases where no obvious changes or trends are identified, the mean of the data across all times for a given job or similar exposure group (SEG) will be used as the concentration estimate.

SEG exposure data that contains censored (below limit of detection) measurements will be analysed using the log-probit regression technique to obtain robust estimates of the data geometric mean and standard deviation. The arithmetic mean of the censored data will then be calculated using the minimum variance unbiased estimator (MVUE). These analytical procedures will be performed with IH DataAnalyst software (Exposure Assessment Solutions, Inc.; oehs.com).

Environmental concentrations of respirable quartz dust prior to the starting date of available monitoring data will be estimated using the following approach. The history of a given job and facility will be examined to identify probable dates for any likely changes in dust concentration based on process changes, dust controls, etc. After that date, the oldest estimates from the available monitoring database will be taken as representative; that is, concentration estimates derived from the available data will be extrapolated back to the point of the change. For dust concentrations preceding such changes, geometric mean concentrations of respirable dust, averaged across all plants in a given industry segment in the study and broken down by the various production areas, will be calculated and assumed to be representative for a given work area. These industry-segment-wide estimates will be adjusted individually for the expected percentage quartz prevalent in the dusts from a particular plant as an estimate of the concentration of RQ.

For reported jobs in which no specific sampling was done and no specific information on the job's tasks is available (for example, "labor" and "utility"), dust concentrations will be assumed to be equal to the overall mean of the estimates for all production jobs in the facility.

To the extent that other sources of exposure data for the industries involved can be identified, a comparison will be conducted with the company data which form the basis of the exposure assessment. The methods used in the proposed exposure assessment have been utilized

successfully in past epidemiologic investigations in the industrial sand industry and have been vetted through peer review and open publication. An internal validation of the exposure assessment approach and results was previously done by relating the exposure estimates to observed silicosis/silico-tuberculosis mortality rates. A strong and statistically significant exposure-response suggested there was no differential misclassification in the exposure assessments. Unfortunately, a "gold" reference standard would be needed to demonstrate absence of non-differential misclassification in the exposure estimates, and this does not exist. Nonetheless, any non-differential misclassification would only attenuate the strength of any true relationship thus reducing the power of the study to detect effects but would not result in any inherent bias in the exposure-response relationship observed.

Protective equipment: The use of respiratory protective devices by workers is an important modifier in constructing the job exposure matrix. Assigned exposures will be adjusted for attenuation through use of respiratory protective equipment for those time periods during which well-designed and enforced respiratory protection programs were in effect. The approach to adjustment of the exposure estimates for respirator use will depend upon the nature of the specific information available regarding respirator use. For those exposure data in which individual samples are flagged for respirator use, the assigned exposure concentration for that sample will be reduced by the workplace protection factor:

$$C' = \frac{C}{WPF}$$

Where C' is the RQ exposure concentration adjusted for respirator use, C is the measured environmental exposure level, and *WPF* is the assigned workplace protection factor. A *WPF* of 5 will be used in this calculation based on reported workplace protection factors afforded by air-purifying respirators for small particle and vapor hazards.[9]

All samples taken prior to the establishment of a respiratory protection program and those subsequent samples which indicated no use of respiratory protection during the monitoring period will not be adjusted under the assumption that the environmental exposure level would be representative of the resulting inhalation exposure. Subsequently, the overall exposure averages will be computed for each job or similar exposure group using the combined adjusted and unadjusted data.

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[9] Nicas M, Neuhaus J: Variability in respiratory protection and the assigned protection factor. J Occup Environ Hyg 1:99, 2004.

For some plants, recording of respirator use in the exposure database was delayed for some time after the institution of a respiratory protection program. In these cases, estimates of frequency of use of respirators for a given job title are obtained from the observed frequency for the time period after which the information is included in the exposure database, under the assumption that it is representative of prior usage patterns. The observed frequency is taken as the proportion of samples that are flagged for respirator use for a given job. This frequency is then used in conjunction with the assigned workplace protection factor to adjust the average exposure levels as follows:

$$C' = C(1 - f) + C\left(\frac{f}{WPF}\right),$$

Where C' is the assigned exposure concentration to RQ adjusted for respirator use, C is the average measured environmental exposure concentration, f is the observed frequency of respirator use ($0 \leq f \leq 1$), and WPF is the protection factor ($WPF = 5$). This formula will be applied to all the exposure data covering the period starting with the date of institution of the respiratory protection program at a given plant. Prior to that date, the exposure data will not be adjusted for respiratory protection and the unadjusted measured environmental exposures will be taken as representative of the actual inhalation exposures of the workers.

Because of the numerous assumptions required to perform the exposure adjustments, a sensitivity analysis will be carried out to investigate whether various assumptions on past exposures and respirator use result in different estimated effect sizes. For example, respirator workplace protection factors of 1 (no protection or frequency of use equal 0), 5, and 10 and frequency of use of 100% will be considered and exposure effects under each condition will be determined and compared.

Individual cumulative and average exposures: For each of the workers in the study, their individual cumulative and average exposures to RQ will be calculated for any specified year of employment by integrating their unique job history with the respective job-time-exposure matrix. Thus,

$$D = \sum C'_i \times t_i$$

and

$$C'_{avg} = \frac{D}{\sum t_i}$$

Where D is the cumulative exposure dose to RQ, C'_i is the assigned respirator –adjusted exposure level from the job exposure matrix for time segment, t_i, and C'_{avg} is the average exposure level.

D. Statistical Analyses

Aim 3. Conditional logistic regression will be used to assess the association between the relative risk of radiologic silicosis and cumulative exposure, average exposure and duration of exposure to RQ. Use of this analysis with nested case-control data produces estimates that are comparable to the hazard ratios obtained from Cox regression of data from the entire cohort. [10] For each set of matched cases and controls, the exposure metrics will be computed by accumulating exposures from the date of first employment to the date of radiologic detection for the case, as well as by lagging exposures to exclude those that were too recent to have a radiologically detectable effect. Lags of 5, 10 and 15 years will be examined. In the primary analyses, the exposure metrics will be included in the regression models as continuous variables. However, auxiliary analyses with the exposure metrics as categorical variables will be conducted to examine the validity of assumption that the logarithm of relative risk is linearly related to exposure. In some analyses, category cut points will be based on the quintiles of the combined distribution of the exposure metric for the cases and controls, but quantile-quantile (Q-Q) plots will also be examined by obtaining odds ratios for all possible cut points.[11] If the results indicate the linear assumption might not be valid, additional analyses will be performed using appropriate transformations of the continuous exposure metrics to fit alternative exposure-response models. If an exposure-response relationship cannot be modelled by transforming the exposure variable, cubic spline functions will be used.[12]

Aim 4. Other exposure metrics will be used in conditional logistic regression analyses to examine the potential existence of exposure thresholds, as well as to assess the effects of the timing of exposure and changes in exposure intensity over time. In the simpler of these analyses, maximum likelihood estimates of thresholds for cumulative exposure and average exposure intensity will be obtained by iteratively re-computing these variables using differing threshold values, so that exposures below the threshold are assigned a value of zero, and fitting the regression model to find the value of the threshold that maximizes the likelihood. This method will be implemented using Proc NLP in SAS/OS. More complex exposure metrics will be used to characterize the relationship between the relative risk of radiologic silicosis and exposure

[10] Breslow NE, Lubin JH, Marek P, Langholz B: Multiplicative models and cohort analysis. J Am Stat Assoc 78:1-12, 1983

[11] Wartenberg D, Northridge M: Defining exposure in case-control studies: a new approach. Am J Epidemiol 133:1058-1071, 1991.

[12] Heinzl H, Kaider A: Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. Compute Methods Programs Biomed 54:201-208, 1997.

intensity, including assessments of a potential intensity threshold and the effects of changes in intensity over time.[13] The general form of these exposure metrics is:

$$z(u) = \sum_{t=1}^{u} g(x_t) d_t \, w(t,u)$$

where z(u) is the total exposure accumulated through time u, x_t is the exposure intensity during time interval t, d_t is the length of the time interval, w(t,u) is a weight reflecting the timing of exposure, and $g(x_t)$ is a function of x_t. The function $g(x_t)$ can be used to model an intensity threshold as well as to model exposure-response relationships in which the effect of intensity is not proportional to its magnitude. Estimates of thresholds and other model parameters will be obtained by iteratively maximizing the likelihood as described above. Candidate functions for $g(x_t)$ and initial parameter estimates will be identified by fitting multivariate models to examine the effects of the duration and timing of work at differing exposure intensities.

Aim 5. The best fitting exposure-response models identified in Aims 3 and 4 will be used to estimate the absolute risk of radiologic silicosis for RQ exposures of 0.05, 0.1 and 0.2 mg/m^3 over a working lifetime. This will be done using the method described by Langholz and Borgan for nested case-control data.[14] Briefly, their estimator is based on the regression coefficients obtained from conditional logistic regression analysis and information about the number of individuals who are at risk at the time each case is diagnosed with radiologic silicosis. The number of individuals at risk will be obtained as part of the sampling protocol for matching cases to controls. Likelihood ratio tests will be used to compare the fit of the exposure-response models derived in Aims 3 and 4, and the regression coefficients for the best fitting models will be used for estimating absolute risk. Standard error for the absolute risk estimates will be computed as described by Langholz and Borgan and will be used to construct 95% confidence intervals.

Aim 6. Sequential X-ray data from radiologic silicosis cases will be analyzed to examine the factors associated with disease progression. All chest X-rays obtained on these individuals will be classified into one of the categories of the 12-point classification scale and progression of disease will be defined as a change to a more severe classification. Cox proportional hazard regression will be used to model time until first progression of disease (first change to a more

[13] Vacek PM: Assessing the effect of intensity when exposure varies over time. Stat Med 16:505-515, 1997

[14] Langholz B, Borgan O: Estimation of absolute risk from nested case-control data. Biometrics 53:767-774, 1997.

severe classification). Predictors in the model will include age, exposure and severity classification at the time radiologic changes consistent with silicosis are first detected. Exposure after detection of radiologic silicosis will be included as a time-varying predictor. The probability of progression and its relationship to exposure, adjusting for other possible determinants, will also be assessed using data from all X-rays obtained after first detection of radiologic silicosis and fitting hierarchical logistic regression models with subject as a random effect. In these analyses progression at the time of each X-ray will be defined as yes or no based on whether or not the disease severity classification is higher than observed on any of the previous X-rays. Sensitivity analyses will be performed to determine if the resulting determinants of progression are related to various definitions of progression (i.e. one, two or three stage progression). In addition, the rate and degree of progression will be examined by plotting the 12-point scale outcome against exposure over time for individual workers and factors associated with progression will be assessed using mixed effects regression models. In these analyses the value of the 12-point scale outcome from each X-ray will be use as a continuous, ordinal or categorical outcome and will be modeled as a function of the fixed effects of time, exposure, age and other potential covariates. Subject will be included in the model as a random effect to allow for subject-specific differences in the rate of progression and to account for correlations between repeated measurements from the same individual.

Aim 7. The exposure response-estimates for risk of disease and probability of progression derived from this study will be compared to those of other published studies. Exposure-response plots analogous to those available from other studies will be presented for the models derived in this study. For published studies that provide information about the variance of risk and/or relative risk estimates, differences between those estimates and the ones obtained from our study will be assessed by Z-tests.

E. Statistical Power

The statistical power to detect a significant association between radiologic silicosis risk and a continuous exposure metric using conditional logistic regression was conservatively estimated by computing the power to detect a trend in risk over five exposure categories. Assumptions about the distribution of exposures were based on data from prior studies of industrial sand workers and categories were defined as the quintiles of the combined distribution for cases and controls. Because cases and controls will be matched on year of hire and plant, both of which are likely to be associated with exposure, we examined different scenarios about the correlation between the matching variables and exposure. We also examined alternative assumptions about the sampling fraction for the controls in each exposure category. Power was based on 54 cases, 3 matched controls per case, and a 1-tailed significance level of 0.05. Under more favorable scenarios (low correlation between the matching and exposure variables and a moderate decrease in the control sampling fraction with increasing exposure) the study will have at least 80% power to detect a significant trend if risk increases over the five exposure categories

to an OR of 3.1 for the highest exposure category compared to the lowest. Under less favorable scenarios, a significant trend will be detected with 80% power if risk increases to an OR of 3.6 for the highest exposure category. Calculations were performed using Egret Siz statistical software (Cytel Software Corporation). This is a conservative estimate because analyses based on a continuous exposure variable will have better statistical power to detect a quantitative exposure-response relationship than a trend test across exposure categories. In addition, the power calculations were based on the minimum number of cases expected in the study (those identified from surveillance reading of the X-rays) and additional cases may be identified when the X-rays are re-read.

Power calculations for the progression analyses were based on X-ray data from the companies' case registries, which indicated that the number of X-ray classifications after first detection of radiologic silicosis ranged from 2 to 19, with an average of 9 per case. About 80% of the cases had least one X-ray showing progression and time to first progression ranged from 1 to 13 years. The power of Cox regression to detect an association between a continuous exposure measure and time to first progression was estimated based on preliminary data indicating that cumulative exposures across all plants are lognormally distributed with a geometric mean and standard deviation of 94 $\mu g/mg^3$ and 7.5 $\mu g/mg^3$, respectively. With 54 cases and a 1-sided significance level of 0.05, the study will have at least 80% power to detect a significant association if relative risk increases 21% (RR = 1.21) for each unit increase in the natural logarithm of cumulative exposure, which corresponds to a 2.72 fold increase in cumulative exposure (e.g. 10 $\mu g/mg^3$ versus 27.2 $\mu g/mg^3$). For the mixed effects regression analyses to assess progression using all available X-rays after first detection of radiologic silicosis for each case, we estimated that the study will have 80% power to detect an association corresponding to a correlation of 0.30 between a continuous exposure measure and progression, even if there is considerable between-person variability (twice the value of the transformed correlations statistics) in response to exposure.

III. Timetable of Activities [15]

Task	Weeks	Rev Wks	Cum Wks	Rev Cum Wks	Radiological Classification Study Tasks	Exposure Reconstruction Tasks
1	6	8	6	8	Companies provide the last film in the surveillance series for all eligible workers (~ 1,670). A research team member will visit the companies and take possession of the films. Develop data collection forms and obtain IRB approval, and hire personnel. *[All of the forms etc. have to be completed before submission to the Institutional Review Board]*	Obtain plant history and process information. Companies provide current exposure monitoring databases.
2	3	4	9	12	Prepare films of the ~ 1,670 eligible workers, ILO forms, and conduct case identification chest film reading in Morgantown, WV over a 5-day period.	
3	3	4	12	16	Select three matched controls for each of the cases by random sampling from all cohort members at the same plant with similar dates of birth. Controls must also have worked beyond the case's date of radiologic diagnosis to increase the chance that they will have an X-ray on or after that date.	
4	2	3	14	19	Companies pull the control films identified by the researchers and ***all*** films in the surveillance film series for	

[15] The timetable will begin after IRB approvals are received and will be adjusted for delays for progress reviews initiated by the sponsors, and for other circumstances outside of the control of the research team.

					cases identified in the identification chest film reading. A research team member will visit the companies and take possession of the films.	
5	2	3	16	22	Assemble all films (~ 750) in the surveillance series in temporal order for identification of the first film with changes consistent with pneumoconiosis. JEP will classify the films to determine the first film consistent with changes consistent with pneumoconiosis.	
6	4	5	20	27	Label ≈ 1,075 chest X-rays for cases, controls, progression (surveillance) films and quality assurance films with ID numbers, and redact any identification information Label ~ 3,225 ILO forms with ID numbers and radiologist's initials. Randomly batch the labeled X-rays into groups of ~200 chest X-rays.	Companies provide individual worker job histories for cases and controls.
7	2	3	22	30	Conduct the classification study over two 3-day periods (weekends) with the 3 radiologists in a central location. The facility will have 3 separate rooms, each with light boxes, available for each radiologist. Pre-labeled, dated and initialed ILO forms will be clipped to the films. Provide a recorder to mark each ILO form according to the radiologist's classification. As classification forms are completed researchers will check for completeness	Complete dictionary of job codes and definitions.
8	4		26	34	.	Complete coding of individual work histories and construct a database for

						linking with the job/time/exposure matrix. Verify a randomly selected 10% of the work histories from review of company records.
9	4		30	38		Identify similar exposure groups. Complete primary and alternative adjustments of exposure for respirator usage by plant, department, and job (primary scenario: APF = 5 and f = observed; 4 alternative scenarios: APF = 1 and f = 0, APF = 5 and f = 1, APF = 10 and f = observed, APF = 10 and f = 1). Calculate average adjusted exposures by SEG.
10	4	7	34	45	Verify ILO form completeness and send forms to Vermont Team for data entry and analyses.	Complete job/time/exposure matrices (JTEM). Merge individual job histories with JTEM. Calculate yearly exposures for each worker under each respiratory protection scenario for entire work history. Compute metrics that reflect exposure up to the time of silicosis for each case and its matched controls
					Data Analyses Tasks and Report Preparation	
11	2		36	47	Enter X-ray classification data from the ILO forms.	
12	2		38	49	Process data to compare radiologists' classifications, determine median classifications, assess reliability and quality control.	
13	2		40	51	Create data files for statistical analyses	
14	12		52	63	Perform statistical analyses 1. Relative risk/Exposure Response 2. Estimation absolute risk	

					2. Progression/Exposure Response 3. Comparison of results to other published results.
15	2		54	65	Summarize results using tables and figures.
16	5		59	70	Prepare a final draft report of the study.
17	2		61	72	Send the final report to sponsors for a review of technical accuracy.
18	2		63	74	Publish final report and submit to sponsors.
19	4		67	78	Prepare manuscript(s) for the medical literature

IV. Research Investigators

John E. Parker, M.D., FAACP, FCCP is professor and the chief of pulmonary and critical care medicine at Robert C. Byrd Health Sciences Center, West Virginia University. Dr. Parker is the Principal Investigator for the study described in this protocol. He is a board certified internist and pulmonologist and a National Institute for Occupational Safety and Health (NIOSH) certified B-reader. In his current position he cares for patients at that hospital, teaches medical students and oversees the pulmonary and critical care department. From 1976 through 1998, he held various positions with the United States Public Health Service, including several positions at NIOSH. While at NIOSH he administered, the NIOSH B Reader certification program, served as the chief of the clinical investigations branch of respiratory disease studies, and served as the chief of the epidemiological investigations branch of respiratory disease studies. He has conducted research in occupational lung diseases and has published peer-reviewed articles on the respiratory system, lung disease and chest imaging issues. He has published articles and made many invited presentations about the ILO classification system, the NIOSH B Reader program, high resolution CT scans and imaging techniques. Dr. Parker will serve as co-principal investigator and radiology consultant for the radiology classification studies.

Roy J. Rando, Sc.D., *C.I.H.* is Professor and Vice Chair in the Department of Global Environmental Health Science in the Tulane University School of Public Health and Tropical Medicine and Adjunct Professor of Environmental Medicine in the School of Medicine. He is a certified industrial hygienist. He is a leading expert in the field of exposure assessment, has developed numerous job exposure matrices in support of epidemiologic investigations of worker health, and has participated in studies of occupational and environmental respiratory disease for more than 30 years, including studies of morbidity and mortality of lung cancer, silicosis and renal disease in industrial sand workers.

Pamela M. Vacek, Ph. D. is a Research Associate Professor in the Departments of Medical Biostatistics and Pathology at the University of Vermont College of Medicine. She has more than 30 years of experience working on a wide range of biomedical research as an epidemiologist and biostatistician. Much of her research has focused on the health effects of mineral dust and chemical exposures, particularly as they related to cancer. She has collaborated on several previous studies of the Vermont granite industry and was the principal investigator for a recently completed mortality study of the industry.

Robert E. Glenn, Sr., M.P.H. C.I.H. is an industrial hygienist and principal of Glenn Consulting Group, LLC. He is a retired commissioned officer in the U.S. Public Health Service where he was Director of the Division of Respiratory Disease Studies of the National Institute for Occupational Safety and Health. He has published articles on the dust-related diseases, is often invited to speak at scientific meetings on silicosis prevention, and has served as an adviser to the

World Health Organization and the Pan American Health Organization. He will be responsible for directing all activities of the radiology classification studies and project administration.

Mike Desarno, M.S. has worked as a biostatistician in the Medical Biostatistics Dept. at the University of Vermont since January, 2010, providing data management and statistical support for a variety of research projects. As a graduate student in statistics at the University of Vermont he received the 2006 Graduate Student Award for Achievement of Excellence in Statistics and was elected to Mu Sigma Rho National Statistical Honor Society. He has a B.S. in electrical engineering (Cornell, 1987) and worked for 21 years in the semiconductor industry as a process engineer for IBM (1988-1995) and Axcelis Technologies from (1995-2009).

V. Projected Costs [16]

Personnel Costs			Revised Budget
John Parker, Principal Investigator, WVU Medical School	400 hrs @ $225/hr	$90,000	$90,000
Robert Glenn, Glenn Consulting Group	(~~600~~) 720 hrs @ $225/hr	135,000	162,000
Pamela Vacek, Biostatistician, U of Vermont	400 hrs @ $125/hr	50,000	50,000
Mike Desarno, Biostatistician Assistant, U of Vermont	1100 hrs @ $80/hr	88,0000	88,000
Roy Rando, Industrial Hygienist, Tulane University	0.15 FTE	30,137	30,137
TBD, Industrial Hygiene Assistant	0. 5 FTE	35,696	35,696
Film Study Coordinator	(~~120~~) 144 hrs @ $25/hr	3,000	3,600
Film Study Recorder	(~~80~~) 96 hrs at $15/hr	1,200	1,440
Film Study Recorder	(~~64~~) 76 hrs at $15/hr	960	1140
Film Study Recorder	(~~64~~) 76 hrs at $15/hr	960	1140
	Personnel Total	$434,953	$463,153
Other Direct Costs			

[16] This budget does not reflect professional fees and travel related costs to participate in progress reviews of the study initiated by the sponsors.

X-Ray Reader Cost – Identification of Cases (1,670 eligible workers X 2 + 60 classification disagreements = ≈ 3,400 ILO Classifications) (2,051 film classifications X 2 + 70 classification disagreements = ~ 4,172 ILO Classifications)	51,000	62,580
X-Ray Reader Cost – Film classifications for cases, control, serial progression and quality assurance films (1,075 X 3 = ~ 3,225 ILO classifications X $50 = $161,250)	161,250	161,250
X-Ray Shipping Cost	1,500	1,800
Office Supplies and Computer Supplies	1,100	1,320
Xeroxing ILO Forms	1,500	1,800
Data Entry	18,000	18,000
Office and computer supplies, Tulane University	650	650
X-Ray Reader & Reading Team Travel & Lodging	11,700	14,040
Central Reading Study Meeting Cost	10,000	12,000
PI and Consulting Scientist Travel	12,150	14,580
Tulane Office Supplies	1,165	1,165
Tulane Travel	3,500	3,500
Tulane IRB Fee	1,000	1,000
GCG IRB Fee	750	750

Other Direct Costs Total	$275,625	$294,435
Indirect Costs		
Tulane University Indirect Costs	$17,875	0
Total Direct Costs	$728,453	$757,588